Lung Cancer Risk and Radiation Dose Among Women Treated for Breast Cancer

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Background: **Evidence shows ionizing radiation can cause lung cancer, but few studies have quantified risk in relation to radiation dose.** ***Purpose:*** **This study evaluated the long-term risk of lung cancer among women treated with radiation for breast cancer.** ***Methods:*** **In this case-referent study, the Connecticut Tumor Registry was used to identify women diagnosed with histologically confirmed invasive breast cancer between 1935 and 1971 who survived for at least 10 years (8976) and to ascertain lung cancers occurring in this group between 1945 and 1981. Seventy-six cases of lung cancer were identified; however, 15 cases did not meet the criteria for inclusion. For the 61 remaining lung cancer case patients and 120 reference subjects (selected from the same registry and matched according to race, age at breast cancer diagnosis, year of breast cancer diagnosis, and survival without a second primary tumor), hospital charts were reviewed to collect medical history and radiotherapy information. A medical physicist estimated radiation dose to different segments of the lungs on the basis of radiotherapy reports and experimental simulations of treatments.** ***Results:*** **For these 10-year survivors of breast cancer, the overall relative risk (RR) of lung cancer associated with initial radiotherapy for breast cancer was 1.8 (95% confidence interval [CI] = 0.8-3.8), and the RR increased with time following treatment. The RR for periods of 15 years or more after radiotherapy was 2.8 (95% CI = 1.0-8.2). Mean dose was 15.2 Gy to the ipsilateral lung, 4.6 Gy to the contralateral lung, and 9.8 Gy for both lungs combined. The excess RR was 0.08 per Gy, based on average dose to both lungs, and 0.20 per Gy to the affected (cancerous) lung.** ***Conclusions:*** **Breast cancer radiotherapy regimens in use before the 1970s were associated with an elevated" lung cancer risk many years following treatment. The estimated risk coefficients are lower than those reported for atomic bomb survivors. The lower than expected risk might be attributable to high-dose cell killing or the fractionated nature of the exposure.** ***Implcations:*** **Approximately nine cases of radiotherapy-induced lung cancer per year would be expected to occur among 10000 women who received an average lung dose of 10 Gy and survived for at least 10 years. Current radiotherapy for breast cancer results in less extensive exposure of the lungs in comparison to treatments of years past, and the risk of secondary lung cancer need not play a major role in clinical decisions regarding treatment for breast cancer. Nonetheless, efforts to reduce unnecessary exposure of the lungs and heart should continue to further reduce possible adverse radiation effects. [J Natl Cancer Inst 86:983-988, 1994]**

There is ample evidence that lung cancer can be caused by ionizing radiation *(1,2),* but few studies have quantified the relationship between radiation dose and lung cancer risk. Only the studies of atomic bomb survivors *(3,4),* underground miners *(2,5),* and Hodgkin's disease patients *(6)* have provided information on radiation dose–response to date. Radiogenic lung cancer also has been repotted among patients treated for benign conditions such as ankylosing spondylitis *(7)* and peptic ulcer *(8),* but dose–response evaluations were not possible. The experience of women treated for breast cancer in previous decades is potentially instructive, because doses to the lungs often were high, treatment data necessary for dosimetry are available, sufficient time has elapsed for radiation effects to be detectable, and the number of long-term survivors is large. Previous cancer registry studies *(9,10)* have reported excesses of lung cancer among women irradiated for breast cancer.

In the present study, we used a case-referent approach to evaluate long-term risk of lung cancer in relation to radiation dose within a cohort of 27016 women with breast cancer reported to the Connecticut Tumor Registry *(9).*

Subjects and Methods

Study Population

The Connecticut Tumor Registry *(11)* was used both to identify the underlying population of breast cancer patients and to ascertain subsequent lung cancers. Included were women who were diagnosed with histologically confirmed invasive breast cancer between 1935 and 1971, whose cancers were documented in the Connecticut Tumor Registry, and who were followed for at least 10 years after diagnosis, There were 8976 such women.

Incident cases of primary lung cancer were ascertained for this population for the period 1945-1981. Seventy-six lung cancer case patients were identified. Ten cases were excluded for the following reasons: Medical records did not indicate the presence of a lung rumor (n = 3), patient had metastatic disease and lung was not known to be the primary site (n = 5). lung cancer was the third primary cancer (n = I). and initial diagnosis of breast cancer was not confirmed (n = 1). This left 66 cases available for analysis.

Two reference subjects were selected for each lung cancer case patient, matched on race. age at breast cancer diagnosis, calendar year at breast cancer diagnosis. and survival (± 2 years) without a second primary cancer for at least as long as that of the corresponding case patient. In one instance, tolerances had to be extended to ± 5 years for age and year of diagnosis to obtain a match. Refer-

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See "Notes" section following "References."'

ence subjects were selected from among a pool of 1189 women with breast cancer enrolled as controls in a previous study *(12).*

Some patients had received radical mastectomy only, and others had received mastectomy plus adjuvant radiotherapy. Hospital medical and radiotherapy records were reviewed to learn which lung cancer case patients and reference subjects had received radiotherapy for their breast cancer. All 36 hospitals in Connecticut agreed to allow access to their medical records for this study. Radiation treatment data were photocopied for later use in estimating dose to the lungs. Information also was recorded, as available. about current and past smoking habits. but such data proved to be sparse. Because history of radiotherapy for primary breast cancer could not be determined for five case patients and two reference subjects. they were omitted from the analysis. Analyses reported below are based on data for 61 case patients and 120 reference subjects.

The distribution of the lung cancer cases by histopathologic category was as follows: adenocarcinoma (n = 20), squamous ceil carcinoma (n = 8), large-cell carcinoma (n = 4), small-cell carcinoma (n = 14). undifferentiated or anaplastic carcinoma (n = 2), and unknown histopathology (n = 13). of the 13 cases with unknown histopathology, tumor registry records noted that seven were microscopically confirmed, but the pathology report was not available: an additional four were confirmed by radiology report. one was supported by a clinical diagnosis only. and the method of confirmation for one case was unknown. Of the 20 case patients certified to have adenocarcinoma of the lung, 12 women had no evidence of nodal involvement at the time of breast cancer diagnosis. four had one or more positive nodes, and four had unknown nodal status. Literality was known for 55 of the lung cancers. and the approximate location of the tumor within the lung (main bronchus, upper lobe, middle lobe. or lower lobe) was known for 42 of these cases.

Radiation Treatments and Dosimetry

Adjuvant radiotherapy had been administered following radical mastectomy. h typically consisted of lateral and medial tangential breast fields. anterior and posterior supraclavicular fields, and an anterior internal mammary (mediastinal) field *(12).* The radiation was targeted at regional lymph nodes and involved more extensive lung exposure than occurs with radiotherapy following breast-conserving surgery for localized disease. Even the lung on the opposite (contralateral) side of the body from the breast cancer could receive substantial doses.

Sketches of treatment plans were available for approximately half of the women in the present study who had been given radiotherapy and for about 500 women from a previous study of contralateral breast cancer following radiotherapy for breast cancer *(12).* On the basis of the sketches and descriptions. it was concluded that the upper part of the superior lobe of the lung was included in the posterior supraclavicular fields. The majority of the patients had been treated with either orthovoltage x rays or cobalt-60 γ rays. Such low-energy beams have more head leakage and side scatter than high-energy (e.g.. megavoltage) beams within the region between the edge of a field and approximately 15 cm outside the edge of the field. A large pan of the contralateral lung is near supraclavicular. mediastinal, and anterior chest fields. Many patients had been treated with internal mammary or mediastinal fields, which deliver almost equal doses to both lungs. There was no information in individual treatment records to indicate the use of a beam splitter to reduce contralateral breast and lung dose from tangential fields. The total air or given dose to many fields was in the range of 30-60 Gy. Radiation treatments had been given in multiple fractions. typically 5 days per week for 4-6 weeks.

Radiation doses to the lungs were estimated by a medical physicist (M. Stovall) on the basis of treatment details abstracted from each patient's medical record and experimental measurements. In the treatment simulations. absorbed dose was measured with lithium fluoride dosimeters placed in a three-dimensional matrix in a water phantom. Simulations were repeated for different combinations of field size and beam energy. This measurement system is accurate to within 5%. These measured data were then used in a three-dimensional computer representation of an average-sized patient to estimate absorbed dose to any location within the patient. In the mathematical phantom, the lungs. bronchi, and trachea contained a total of 450 points of calculation. The points were evenly spaced in a three-dimensional grid. and lung doses were computed as equal, weighted averages of the estimated dose to each point. Dose estimates for each patient were based on the calculated dose in the mathematical phantom, renormalized to be consistent with the given dose stated in the individual's treatment record. Information about subsequent radiotherapy for recurrent or metastatic disease was recorded. as available. but only the first course of radiotherapy was included in dose determinations.

Analyses

Logistic regression models *(13)* were used to assess the relationship between radiotherapy for breast cancer and subsequent lung cancer, conditionally on matching variables and other covariates of interest. Likelihood methods were used to estimate the relative risk (RR) and associated 95% confidence intervals (CIS). *P* values were based on likelihood ratio tests. PECAN. a program for conditional logistic regression *(14,15),* was used to fit the models. Dose-response analyses were done in terms of mean dose to both lungs and mean dose to the affected (cancerous) lung. The unavailability of information about tumor site within the lung (lobe or bronchus) for eight case patients who had received radiotherapy for breast cancer precluded analysis in terms of local dose to the site of tumor origin within the affected lung.

Results

Bearing in mind that the study was restricted to 10-year survivors of breast cancer, the average interval from diagnosis of breast cancer to diagnosis of lung cancer was 18 years. The average age at breast cancer diagnosis was 50 years, and the average age at lung cancer diagnosis was 68 years.

Distributions of lung cancer case patients and reference subjects with respect to selected characteristics are shown in Table 1. The majority of the breast cancers in the reference series involved the left breast. The distribution was more nearly balanced among the lung cancer case patients. Lung cancers occurred more often in the right lung than in the left lung, possibly because of the larger size of the right lung. There was no evidence of metastatic breast cancer in most women at the time of diagnosis, as indicated by the absence of nodal involvement (Table 1), and few were given chemotherapy, which was not commonly used prior to the 1970s. Three reference subjects, all of whom were initially treated by surgery only, later were given radiation to the chest or thoracic spine to treat metastatic or recurrent disease; the average interval since breast cancer diagnosis was 7.3 years. No lung cancer case patients were known to have received additional thoracic radiotherapy subsequent to their base-line treatment. Information about cigarette smoking, even at the crude level of ever/never, was missing for 77% of the study subjects.

Twenty-eight percent of the lung cancer case patients and 18% of the reference subjects had had radiotherapy as part of their initial course of treatment (Table 2). Among these 10-year survivors of breast cancer, the overall RR of lung cancer associated with initial radiotherapy was 1.8 (95% CI = 0.8-3.8). The RR increased with time following radiotherapy and was especially high among 20-year survivors (Table 3). The RR for periods of 15 years or more after treatment was 2.8 (95% CI = 1.0-8.2). The RR was higher among women irradiated for breast cancer at ages less than 45 years than among women irradiated for breast cancer at older ages, though the trend in RR with age at exposure was not statistically significant when adjusted for time since exposure (*P* = .17 [two-sided test]). Only one of the lung cancers among women who were irradiated at age 55 years or higher occurred 20 or more years after treatment, the interval during which the RR was highest. However, the RR during years 10-20 after treatment also was higher for women diagnosed with breast cancer at a younger age.

Table 1. Distribution of lung cancer case patients and matched reference subjects with respect to selected characteristics*

Characteristic	Lung cancer case patients (n = 61)		Reference subjects (n = 120)	
	No.	%†	No.	%†
Race				
White	57	96.6	118	98.3
Black	2	3.4	2	1.7
Unknown	2			
Age at breast cancer diagnosis, y				
35-44	15	24.6	30	25.0
45-54	30	49.2	58	48.3
55-72	16	26.2	32	26.7
Year of breast cancer diagnosis				
1936-1949	12	19.7	23	19.1
1950-1959	27	44.2	53	44.2
1960-1971	22	36.1	44	36.7
Time since breast cancer diagnosis, y				
10-14.9	23	37.7	46	38.3
15-19.9	15	24.6	30	25.0
20-36	23	37.7	44	36.7
Breast cancer laterality				
Right only	28	47.5	53	44.2
Left only	30	50.8	67	55.8
Bilateral	1	1.7	0	0.0
Unknown	2			
Lung cancer laterality‡				
Right	29	52.7	—	—
Left	26	47.3	—	—
Unknown	6			
Nodal involvement, No. of positive nodes				
0 (none)	32	71.1	78	74.3
1-3	9	20.0	19	18.1
4-9	4	8.9	6	5.7
≥10	0	0.0	2	1.9
Unknown	16		15	
Other radiotherapy to chest or thoracic spine§				
No	61	100.0	117	97.5
Yes	0	0.0	3	2.5
Chemotherapy for breast cancer‖				
No	59	96.7	109	94.0
Yes	2	3.3	7	6.0
Unknown	0		4	
Smoking habits				
Never smoked	3	21.4	17	63.0
Smoker	10	71.4	9	33.3
Ex-smoker	1	7.1	1	3.7
Unknown	47		93	

*Matching variables included race, age and year at breast cancer diagnosis, and time since breast cancer diagnosis.

†Percentages exclude persons with unknown status for that variable.

‡The location of the tumor within the lung was upper lobe (n = 20), middle lobe (n = 6), lower lobe (n = 13), main bronchus (n = 3), and unknown (n = 19).

§For metastatic or recurrent breast cancer. Includes only radiotherapy given prior to the date of diagnosis of lung cancer for the case in the matched set.

‖Includes only chemotherapy given prior to the date of diagnosis of lung cancer for the case in the matched set.

Table 2. Numbers of lung cancer case patients and reference subjects who were irradiated for breast cancer and estimated RR attributable to radiotherapy

Radiotherapy*	Lung cancer case patients (n = 61)		Reference subjects (n = 120)		RR (95% CI)
	No.	%	No.	%	
No	44	72.1	99	82.5	1.0 (reference)
Yes	17	27.9	21	17.5	1.8† (0.8-3.8)

*Includes only radiotherapy given as part of the initial course of treatment. Three additional reference subjects, but no case patients, are known to have received radiotherapy to the chest or thoracic spine between the date of breast cancer diagnosis and the date of diagnosis of lung cancer for the case patients in the matched set (mean interval, 7.3 years). If these women were counted as "exposed," the RR associated with radiotherapy would decrease (RR = 1.5; 95% CI = 0.7-3.2).

†From conditional logistic regression.

Table 3. RR of lung cancer associated with radiotherapy for breast cancer in relation to time since breast cancer diagnosis, whether the lung cancer was ipsilateral or contralateral to the breast cancer, and age at breast cancer diagnosis

Characteristic	RR	95% CI	No. of lung cancer patients: Total	≥20 y*	P†
Time since breast cancer diagnosis, y					
10-14.9	1.0	0.3-3.1	23	0	$P_{(1)}$ = .07‡
15-19.9	1.4	0.3-6.4	15	0	
20-35.9	5.5	1.3-37.2	23	23	
Lung cancer laterality relative to breast cancer§					
Ipsilateral	2.7	0.7-13.4	16	7	$P_{(1)}$ = .32
Contralateral	1.8	0.7-4.9	36	11	
Unknown	0.7	0.0-5.2	8	4	
Age at breast cancer diagnosis, y					
35-44	3.7	0.7-26.4	15	7	$P_{(2)}$ = .17‖
45-54	2.1	0.8-6.0	30	15	
55-72	0.4	0.0-2.5	16	1	

*Number of 20-year survivors.

†$P_{(1)}$ denotes one-sided test; $P_{(2)}$ denotes two-sided test.

‡Trend for time since diagnosis, adjusted for age at breast cancer diagnosis.

§Case patient with bilateral breast cancer excluded.

‖*P* value (but not the age-specific RRs) is adjusted for time since breast cancer diagnosis. For the interval 10-20 years following treatment for breast cancer, the RRs for the three age groups were 1.8, 0.8, and 0.2, respectively.

The sample was too small to detect possible differences by histopathologic subtype of lung cancer, but the RR was 1.6 for adenocarcinoma (95% CI = 0.4-6.0), 1.4 for squamous cell carcinoma (95% CI = 0.2-12.7), 2.3 for small-cell carcinoma (95% CI = 0.5-1 1.5), and 2.0 for tumors of unknown histopathology (95% Cl = 0.4-10.7). An increasing RR with time following treatment was seen for adenocarcinoma but not for all other tumors of specified histopathologic type combined.

The RR was higher for ipsilateral lung cancer, i.e., cancer arising in the lung on the same side of the body on which the breast cancer occurred (RR = 2.7), than for tumors arising in the lung on the contralateral side (RR = 1.8). However, the difference was not statistically significant, and contralateral lung cancers outnumbered ipsilateral lung cancers (Table 3). Among irradiated reference subjects, the average dose to the ipsilateral lung was 15.2 Gy, and the average dose to the contralateral lung was 4.6 Gy. The mean dose to both lungs combined was 9.8 Gy. Within the ipsilateral lung, the doses to the different lobes and bronchus differed by as much as a factor of four or five.

The use of radiotherapy was more frequent among women with node-positive breast cancer than among women with node-negative breast cancer. Forty-eight percent of reference subjects with one or more positive nodes had been irradiated, but only 3% of those with negative nodes had been given radiotherapy. The average lung dose was higher for reference subjects with positive nodes than for those with negative nodes.

Dose-response data are presented in Table 4. Neither of the representations of lung dose yielded a statistically significant association with RR, and only for dose to the affected lung did a straight-line dose-response model fit better than a model with a simple binary (yes/no) indicator of exposure. Although the slope was not significantly different from zero (*P* = .18 [one-sided test]). results for the affected lung were weakly suggestive of a dose–response relationship. The best estimate of the excess RR would appear to be that based on mean dose to the affected lung, or 0.20 Gy^{-1}. This implies a 20% increase in the RR per Gy. Expressed in terms of mean dose to both lungs combined, the average excess RR was 0.08 Gy^{-1}.

Although it was not possible to control for cigarette smoking, the limited available data did not support the view that the positive association with radiotherapy was attributable to confounding by smoking. With partial adjustment for smoking (never, ever, unknown). the RR associated with radiotherapy changed only marginally, from 1.8 to 2.0: among 20-year survivors, the RR changed from 5.4 to 7.6.

Discussion

This study is unique among studies of lung cancer following treatment for breast cancer in having dosimetry for individual patients and addressing long-term post-treatment experience. The findings are referable to a specific underlying cohort experience, which helps to place the results in perspective.

Limitations of the study include its small size, the lack of information about cigarette smoking, uncertainties in distinguishing recurrent breast cancers from new primary tumors. and incomplete knowledge of the site of origin of tumors within the lung, a problem that is magnified by the inhomogeneous distribution of radiation dose to the lungs.

Although the number of cases was small, and detailed analysis of risks by subgroups was not possible, the case series represents a near census of lung cancers occurring between 1945 and 1981 among Connecticut women who had been treated for breast cancer over a 37-year period and who survived for at least 10 years.

Two observations suggest that confounding by cigarette smoking was not a serious problem. First. based on the 27 women in the reference series for whom information about smoking and radiotherapy was available, the two were not positively associated. and adjustment for smoking based on the limited available data made only a small difference in the estimate of the RR for radiotherapy. Second, in an earlier cohort analysis that included these women and contrasted cancer incidence with that expected on the basis of Connecticut population rates *(9)*, other smoking-related cancers, such as cancers of the oral cavity, bladder, and pancreas, either were not elevated or were elevated only slightly among irradiated 10-year survivors relative to nonirradiated patients.

As with studies of multiple primary cancers in general, the issue arises as to the certainty with which new primary tumors can be distinguished from metastatic or recurrent disease. Because the large majority of primary breast cancers are adenocarcinomas, lung cancers of this histopathologic type are of particular concern *(16)*, along with those tumors for which a histopathologic diagnosis was not available. However, it should be noted that the study was restricted to 10-year survivors of breast cancer and that most of the women had zero positive nodes at the time of breast cancer diagnosis. The RR associated with radiotherapy was similar for adenocarcinoma and other histopathologic types, which are much less likely to represent misclassified breast metastasis. Nonetheless, the possibility of misclassification of disease is an important limitation of this study.

Table 4. RR of lung cancer following treatment for breast cancer, by estimated average radiation dose to both lungs combined and average dose to the affected (cancerous) lung

Lung dose, Gy: Interval	Mean	No. of lung cancer case patients	No. of reference subjects	RR (95% CI)	Excess RR, Gy^{-1} (95% CI)
Average dose to both lungs					0.08 (–0.07-0.22)*
0-0	0.0	44	99	1.0 (reference)	
0.1-4.9	4.1	3	3	1.8 (0.3-9.7)	
5.0-9.9	6.6	7	5	3.1 (0.9-12.0)	
10.0-17.5	13.1	6	12	1.2 (0.4-3.4)	
Unknown	—	1	1	2.1 (0.1-53.2)	
Average dose to affected lung					0.20 (–0.62-1.03)*
0-0	0.0	44	99	1.0 (reference)	
0.1-4.9	2.7	7	11	1.4 (0.5-3.7)	
5.0-9.9	7.0	5	4	3.3 (0.8-16.9)	
10.0-22.6	15.8	3	3	2.4 (0.4-18.6)	
Unknown	—	2	3	1.5 (0.2-9.6)	

*Wald-type CI. Likelihood-based lower confidence bound could not be identified.

Among the atomic bomb survivors, all histopathologic subtypes of lung cancer appeared to be elevated among the more heavily exposed, and the slope of the linear dose–response relationship did not differ significantly by histologic type *(4)*. However, results differed somewhat between males and females. Whereas the excess RR coefficient for males was highest for small-cell carcinoma, the excess RR coefficient for females was higher for adenocarcinoma and squamous cell carcinoma than for small-cell carcinoma, and adenocarcinoma was the most common type of lung cancer among females. These differences between the sexes might reflect, in part, different frequencies of exposure to other carcinogens, since different lung carcinogens have been associated with different distributions of histopathologic types *(17-19)*. Many more Japanese men than Japanese women were cigarette smokers *(20)*, and the background incidence of lung cancer was approximately threefold higher among males than females. In any case, the preponderance of adenocarcinomas seen among the female lung cancer case patients in the present study is compatible with a radiation etiology.

The increasing RR with time following irradiation is noteworthy in light of reports that excess lung cancer mortality among irradiated ankylosing spondylitis patients disappeared after 25 years (7) and that the RR among atomic bomb survivors was relatively constant with increasing time after 1957 (4,21). Inferences about time–response patterns based on the present data should be made with caution, because CIS for the different time intervals overlap, and, the high point estimate for the period 20 years or more following treatment might be a chance occurrence. An increase in the RR with time also might arise spuriously if clinicians are more likely to classify an isolated lung lesion in a patient with a history of breast cancer as being a new primary cancer if it occurs many years after breast cancer diagnosis and if radiotherapy is associated with survival. If, however, the RR truly increases with time following radiotherapy, then the absence of an excess of lung cancer among women aged 55 years or older at the time of radiotherapy might be related to a long latent period and the relative scarcity of 20-year survivors in this group; elderly women might have died of other causes before lung cancers developed or progressed to clinical significance. Data also are compatible with the view that the RR of radiotherapy-induced lung cancer is greater for younger women, although it should be noted that the RR for lung cancer among female atomic bomb survivors did not appear to depend on age at exposure or attained age *(4)*.

It is reassuring that the RR associated with radiotherapy that we observed (1.8) equals the ratio of standardized incidence ratios for irradiated and nonirradiated breast cancer patients from the previous analysis of registry data (2.8/1 .6) *(9)*. The earlier study included breast cancer diagnoses through 1972 and lung cancer diagnoses through 1982—in each case 1 year longer than in our study. The key addition in our study is the dosimetry, which can be used together with data from Harvey and Brinton *(9)* to estimate absolute risks attributable to irradiation. Based on the crude incidence rate among nonirradiated 10-year survivors. the observed RR of 1.8, and an average lung dose of 9.8 Gy for irradiated women, the average excess absolute risk can be estimated as 0.9 per 10^4 person-years–Gy, or slightly less than one radiogenic lung cancer per year per 10 000 women given an average dose of 1 Gy, assuming a linear downward extrapolation from 10 Gy to 1 Gy. This estimate applies only to women who survive 10 or more years following radiotherapy for breast cancer.

Added perspective comes from a consideration of the size of the initial cohort that gave rise to the population experience we sampled. Among 27 016 women treated for breast cancer in Connecticut between 1935 and 1971, 8976 of whom survived for at least 10 years, 66 confirmed or probable lung cancers were observed 10 or more years following treatment. Only 28% of these lung cancer case patients had been irradiated. On the basis of an RR of 1.8, we would estimate that about 44% [(RR - 1)/RR] of the irradiated case patients developed lung cancer as a result of their radiotherapy. This translates to eight radiogenic lung cancers (66 x 0.28 x 0.44) out of the starting population of 27 016 women. Of course, the number of cases would increase with additional follow-up beyond 1981 and had women not died of breast cancer or other causes. The preceding calculations assume that misclassification and confounding were not important.

The risk coefficients we observed are lower than values reported for survivors of the atomic bomb explosions in Japan *(4)*, for whom a linear dose–response relationship was observed, with the excess additive risk estimated as 4.35 per 10^4 person-years-Sv and the excess relative risk estimated as 1.9 per Sv *(4)*. The average dose to the lungs was 0.2 Sv *(4)*. In the present study, the excess RR was estimated as 0.1-0.2 per Gy (or Sv), which is an order of magnitude lower than the corresponding estimate for atomic bomb survivors. Possible reasons for the differences in risk coefficients between populations include the anatomically nonuniform and locally very high doses associated with radiotherapy, the fractionated nature of the radiation exposures, and differences in the prevalence of smoking between Japanese and Connecticut women. Parts of the lung received extremely high and possibly cytotoxic doses of radiation. Radiation pneumonitis and lung fibrosis are known sequelae of breast cancer radiotherapy, and radiotherapy of thoracic cancers is constrained by the sensitivity of the lung to radiation damage *(22,23)*. The generalizability of risk estimates from the present study is limited by the fact that they are expressed in terms of mean lung dose rather than local dose to the region where the tumor developed.

Individual dosimetry is lacking for most other studies of medically irradiated populations in which the lungs received an appreciable dose. A 20% excess of deaths due to lung cancer was observed among ankylosing spondylitis patients, mostly males, given fractionated spinal irradiation *(7)*. Estimates of lung doses for individual persons are not available, but Lewis et al. *(24)* estimated the average dose to the lungs as 1.8 Gy. This mean dose would imply an average excess RR of 0.11 Gy^{-1}. A recent study of patients irradiated for peptic ulcer *(8)* reported an excess RR for lung cancer of 0.66 Gy^{-1} associated with an average dose of 1.8 Gy. Among Hodgkin's disease patients given radiotherapy but not chemotherapy, the RR for lung cancer was positively, but not significantly, associated with radiation dose *(6)*, and an average excess RR can be calculated as 0.18-O.25 Gy^{-1} for lung doses of the order of 2-4 Gy. A limitation of this study *(6)*, however, was the absence of a suitable nonirradiated reference group. Recent studies of Hodgkin's disease patients *(6,25)* have suggested that alkylating agents might also cause lung cancers. Most of the women in the present study had been treated for breast cancer before the advent of chemotherapy. Although this situation means that we could not address these agents as potential lung carcinogens, it also means that radiotherapy and chemotherapy were not confounded.

Results suggest that women who were irradiated for breast cancer in Connecticut between 1935 and 1971 had nearly twice the risk of developing lung cancer 10 or more years later, relative to breast cancer patients who were not given radiotherapy, and the excess risk appeared to increase with time following exposure. Interpretation of these results is tempered by the possibility that some of the lung tumors were misdiagnosed recurrent breast cancers. It nonetheless appears that the high doses of radiation associated with adjuvant radiotherapy as practiced in Connecticut between 1935 and 1971 were associated with a relatively small increase in the risk of lung cancer. Because the exact site of tumor origin within the lung was unknown in many cases, it is unclear whether radiation-induced cancers were primarily within the radiation field or were due to scattered radiation.

Treatment practices for breast cancer have changed considerably since the 1960s, and results do not bear directly on risks associated with current treatments, except insofar as the dose-specific excess risk coefficients are applicable. Besides the increased use of chemotherapy and hormonal therapy in the treatment of systemic disease, radiation treatments have changed as well. Today, breast-conserving surgery followed by local radiotherapy is accepted practice for the treatment of early-stage breast cancer *(26-28)*. Smaller radiation fields are used today than in earlier years, and megavoltage therapy has supplanted orthovoltage treatments *(12)*. Average lung doses associated with such treatments are considerably lower than those experienced by women in the present study, who received regional radiotherapy to the chest wall. With the less extensive lung exposures, the risk of radiogenic lung cancer likely is lower as well. Although reductions in unnecessary lung and heart *(29)* exposure are desirable. concern about the risk of secondary, radiation-induced lung cancer need not play a major role in clinical decisions regarding treatment for breast cancer.

References

(1) National Academy of Sciences: Health risks of radon and other internally deposited alpha-emitters. BEIR IV. Washington. DC: National Academy Press. 1988

(2) National Academy of Sciences: Health effects of exposure to low levels of ionizing radiation. BEIR V. Washington. DC: National Academy Press. 1990

(3) Shimizu Y, Kato H, Schull WJ: Studies of the mortality of A-bomb survivors. 9, Mortality, 1950-1985: Part 2. Cancer mortality based on the recently revised doses (DS86). Radiat Res 121: 120-141, 1990

(4) Thompson DE, Mabuchi K, Ron E, et al: Cancer incidence in atomic bomb survivors. Part II: Solid tumors. 1958-1987. Radiat Res 137:S17-S67, 1994

(5) Wagoner JK, Archer VE, Lundin FE, et al: Radiation as a cause of lung cancer among uranium miners. N Engl J Med 273:18 I -188.1965

(6) Kaldor JM, Day NE, Bell J, et al: Lung cancer following Hodgkin's disease. A case control study. Int J Cancer 52:677-681, 1992

(7) Darby SC, Doll R, Gill SK. et al: Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer 55:179-190, 1987

(8) Griem ML, Kleinemtan RA, Boice JD Jr. et al: Canqer following radiotherapy for peptic ulcer. J Natl Cancer Inst 86:842-849, 1994

(9) Harvey EB, Brinton LA: Second cancer following cancer of the breast in Connecticut. 1935-82. Natl Cancer Inst Monogr 68:99-1 12, 1985

(10) Neugut AI, Robinson E, Lee WC, et al: Lung cancer afier radiation therapy for breast cancer. Cancer 71:3054-3057, 1993

(11) Flarrnery JT, Boice JD Jr, Devesa SS. et al: Cancer registration in Connecticut and the study of multiple primary cancers, 1935-1982. Natl Cancer Inst Monogr 68:13-24, 1985

(12) Boice JD Jr, Harvey EB, Blettner M, et al: Cancer in the contralateral breast after radiotherapy for breast cancer. N Engl J Med 326:781-785, 1992

(13) Breslow NE, Day NE: Statistical methods in cancer research. Volume I—The analysis of case-control studies. IARC Sci Publ 32:5-388, 1980

(14) Lubin JH: A computer program for the analysis of matched case-control studies. Comput Biomed Res 14:138-143, 1981

(15) Preston DL, Lubin JH, Pierce DA: Epicure: Generalized Regression Models for Epidemiologic Data. Seattle: HiroSoft International, 1990

(16) Raab SS, Berg LC, Swanson PE, et al: Adenocarcinoma in the lung in patients with breast cancer. A prospective analysis of the discriminatory value of immunohistology. Am J Clin Pathol 100:27-35, 1993

(17) Saccomanno G, Archer VE, Auerbach O, et al: Histologic types of lung cancer among uranium miners. Cancer 27:515-523, 1971

(18) Lubin JH, Blot WJ: Assessment of lung cancer risk factors by histologic category. J Natl Cancer Inst 73:383-389, 1984

(19) Land CE, Shimosato Y, Saccomanno G, et al: Radiation-associated lung cancer: a comparison of the histology of lung cancers in uranium miners and survivors of the atomic bombings of Hiroshima and Nagasaki. Radiat Res 134:234-243. 1993

(20) Kopecky KJ, Nakashima E, Yamamoto T, et al: Lung Cancer, Radiation and Smoking Among A-Bomb Survivors, Hiroshima and Nagasaki. Technical Report (TR) 2-91. Hiroshima: Radiation Effects Research Foundation, 1986

(21) Preston DL, Kato H, Kopecky K, et al: Studies of the mortality of A-bomb survivors. 8. Cancer mortality. 1950-1982 [published erratum appears in Radiat Res 112:403, 1987]. Radiat Res 111: 151-178, 1987

(22) Gross NJ: Pulmonary effects of radiation therapy. Ann Intern Med 86:81-92, 1977

(23) Travis E: Relative radiosensitivity of the human lung. Adv Radiat Biol 12:205-238, 1987

(24) Lewis CA, Smith PG. Stratton IM, et al: Estimated radiation doses to different organs among patients treated for ankylosing spondylitis with a single course of X rays, Br J Radiol 61:212-220,1988

(25) Swerdlow AJ, Douglas AJ, Hudson GV, et al: Risk of second primary cancers after Hodgkin's disease by type of treatment: analysis of 2846 patients in the British National Lymphoma Investigation. BMJ 304:1137-1143. 1992

(26) Harris JR, Recht A, Connolly J. et al: Conservative surgery and radiotherapy for early breast cancer. Cancer 66(6 Suppl): 1427-1438, 1990

(27) Veronesi U, Luini A, Del Vecchio M, et al: Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. N Engl J Med 328: 1587-1591.1993

(28) Fisher B, Costantino J, Redmond C, et al: Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. N Engl J Med 328: 1581-1586.1993

(29) Cuzick J. Stewart H, Rutqvist L. et al: Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 12:447-453. 1994

Notes

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